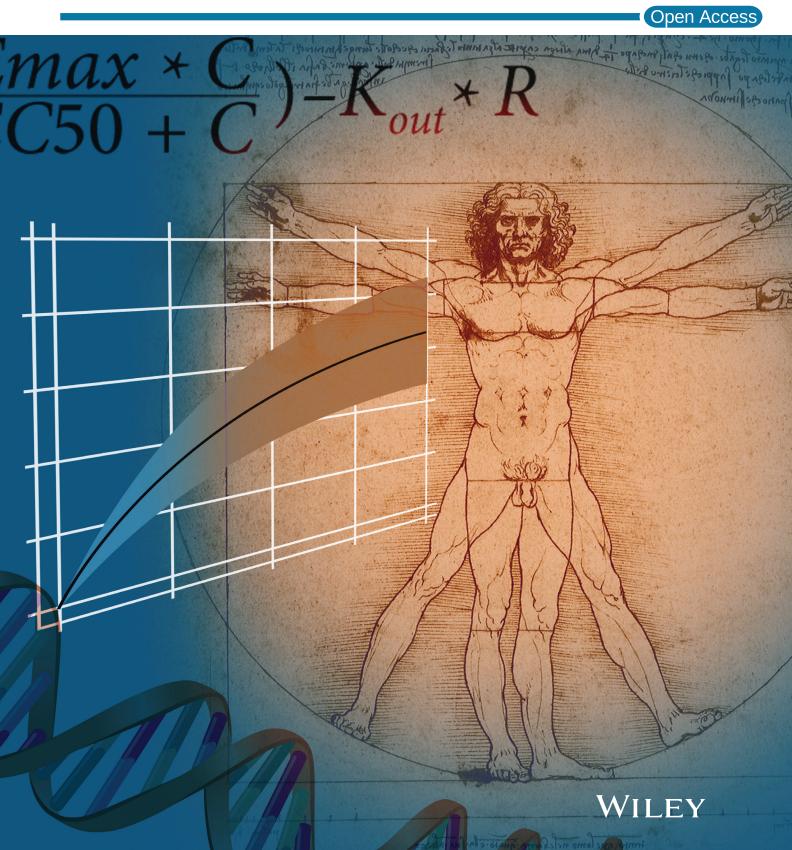
# CPT: Pharmacometrics & Systems Pharmacology



### **CPT: Pharmacometrics &** Systems Pharmacology

## WILEY

#### **Editor-in-Chief**

France Mentré, MD, PhD, School of Medicine of University Paris Diderot,

#### **Deputy Editor-in-Chief**

Lena Friberg, PhD, Uppsala University, Sweden

#### **Associate Editors**

Stephen Duffull, PhD, University of Otago, New Zealand Jonathan French, ScD, Metrum Research Group, Tariffville, CT, USA Douglas A. Lauffenburger, PhD, Massachusetts Institute of Technology, USA Lang Li, PhD, The Ohio State University, USA

Donald Mager, PharmD, PhD, University at Buffalo, State University of New York, USA

Vikram Sinha, PhD, Merck & Co., USA Ping Zhao, PhD, Bill & Melinda Gates Foundation, USA Eric Sobie, PhD, Icahn School of Medicine at Mount Sinai, NY, USA

#### **American Society for Clinical Pharmacology and Therapeutics**

Chief Executive Officer

Sharon J. Swan, Alexandria, VA

**Chief Operating Officer** 

Elise S. Laffman-Johnson, Alexandria, VA

Senior Editorial Coordinators

Rachel Taylor, Alexandria, VA

Julie T. Vo, Alexandria, VA

#### **Editorial Board**

Sandra Allerheiligen, PhD, West Point, PA, USA Ioannis Androulakis, PhD, Rutgers University Surgery, UMDNJ-RWJ Medical School Piscataway Township,

Joseph P Balthasar, PhD, University of Buffalo Buffalo, NY, USA

Jeffrey S. Barrett, PhD, FCP, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Robert Bies, PharmD, PhD, Indiana University Bloomington, IN, USA

Marc Birtwistle, PhD, Clemson University Clemson, SC, USA

Kim L. R. Brouwer, PharmD, PhD, University of North Carolina at Chapel Hill Chapel Hill, NC, USA

Jenny Chien, PhD, Eli Lilly & Co. Clinton, IN, USA David Z. D'Argenio, PhD, University of Southern California Los Angeles, CA, USA

Oleg Demin, PhD, CSO Institute for Systems Biology SPb Moscow, Russia

Paolo Denti, PhD, University of Cape Town Cape Town, South Africa

Hartmut Derendorf, PhD, University of Florida Gainesville, FL, USA

James M. Gallo, PharmD, PhD, Albany College of Pharmacy and Health Sciences, Albany, NY, USA

Christine Garnett, PhD, US Food and Drug Administration, Silver Spring, MD, USA

David Gavaghan, PhD, University of Oxford Oxford, United Kingdom

Ekaterina Gibiansky, PhD, QuantPharm LLC North Potomac, MD, USA

Pascal Girard, PhD, Merck Institute for Pharmacometrics -Merck Serono S.A.Lausanne, Switzerland

Manish Gupta, PhD, FCP, GenMab; Princeton, NJ, USA Bart Hendriks, PhD, Merrimack Pharmaceuticals

Cambridge, MA, USA Nicholas H.G. Holford, MBChB, The University of Auckland Auckland, New Zealand

Brett Howell, PhD, The Hamner-UNC Institute for Drug Safety Sciences Research Triangle Park, NC, USA

Kristin Karlsson, PhD, Uppsala University Uppsala, Sweden

Mats Olof Karlsson, PhD, Uppsala University Uppsala, Sweden

Ron Keizer, PhD, InsightRX San Francisco, CA, USA

Terrence Kenakin, PhD, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA

Steven E. Kern, PhD, Bill & Melinda Gates Foundation Seattle, WA, USA

Andrzej Kierzek, PhD, Certara QSP; Sheffield,

Hiroaki Kitano, PhD, The Systems Biology Institute Tokyo, Japan

Charlotte Kloft, PhD, Freie Universitaet Berlin

Joerg Lippert, PhD, Bayer Healthcare Pharmaceuticals Leverkusen, Germany

Phil Lowe, PhD, Novartis Pharma AG Basel, Switzerland

Wei Lu, PhD, Peking University/Pfizer Pharmacometrics Beijing, China

Efthymios Manolis, MSc, European Medicines Agency London, United Kingdom

Peter Milligan, PhD, Pfizer Global Research and Development

London, United Kindgdom

Diane R Mould, PhD, FCP, Projections Research Inc. Phoenixville, PA, USA

Cynthia J. Musante, PhD, Pfizer Worldwide Research & Development, Cambridge, MA, USA

Jerry Nedelman, PhD, Novartis Pharmaceuticals Corporation East Hanover, NJ, USA

Kyungsoo Park, MD, PhD, Yonsei University College of

Seoul, Republic of Korea Marc Pfister, MD, FCP, University of Basel Rasel Switzerland

Jose Pinheiro, PhD, Johnson and Johnson Pharmaceutical Research Raritan, NJ, USA

Saroja Ramanujan, PhD, Genentech; South San Francisco, CA, USA

Benjamin Ribba, PhD, F. Hoffman-La Roche, Basel, Switzerland

Amin Rostami-Hodjegan, PharmD, PhD, University of Manchester

Manchester, UK Malcolm Rowland, DSc, PhD, University of Manchester Manchester, United Kingdom University of California, San Francisco

San Francisco, CA, USA Julio Saez-Rodriguez, PhD, RWTH Aachen University, Radojka Savic, PhD, University of California Oakland CA, USA

Stephan Schmidt, PhD, University of Florida Orlando, FL, USA

Virginia D. Schmith, PhD, FCP, GlaxoSmithKline Zebulon, NC, USA

Brian Smith, PhD, Novartis Institutes of Biomedical Research, Inc. Cambridge, MA, USA

Peter Sorger, PhD, Harvard Medical School Cambridge, MA, USA

Joe Standing, PhD, University College London London, United Kingdom

David Strauss, MD, PhD, US Food and Drug Administration

Silver Spring, MD

Yuichi Sugiyama, PhD, Riken Innovation Center Sugiyama Laboratory Yokohama, Japan

Hiroshi Suzuki, PhD, The University of Tokyo Hospital Tokvo, Japan

Joel Tarning, PhD, Mahidol-Oxford Tropical Medicine Research Unit Bangkok, Thailand

Nicholas Tatonetti, PhD, Columbia University New York, NY, USA

Iñaki F. Trocóniz, PharmD, PhD, University of Navarra Pamplona, Spain

Natal van Riel, PhD, Eindhoven University of Technology, Eindhoven, the Netherlands

An Vermeulen, PhD, Janssen Research and Development Beerse, Belgium

Paolo Vicini, PhD, MBA, MedImmune, Cambridge, United Kingdom

Alexander A. Vinks, PharmD, PhD, FCP, University of Cincinnati, College of Medicine Cincinnati, OH, USA

Sandra A.G. Visser, PhD, GlaxoSmithKline, King of Prussia, PA, USA

Hua Xu, PhD, University of Texas Health Science Center Houston, Texas, USA

Paul B. Watkins, MD, Institute for Drug Safety Sciences, Eshelman School of Pharmacy University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

Ping Zhang, PhD, IBM T. J. Watson Research Center Yorktown Heights, NY, USA

CPT: Pharmacometrics & Systems Pharmacology (PSP) is an official open access journal of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and International Society of Pharmacometrics (ISoP).

CPT: Pharmacometrics & Systems Pharmacology is a cross-disciplinary journal devoted to publishing advances in quantitative (e.g., modeling and simulation) methods as applied in pharmacology, physiology and therapeutics in humans. The journal welcomes original research articles, reviews and tutorials that bridge the following areas: pharmacometrics, modeling and simulation as applied to the design and evaluation of clinical trials, systems pharmacology modeling, particularly with a mechanistic link to human (patho)physiology, disease modeling, "population" or mixed-effects pharmacokinetics and pharmacodynamics (PKPD) modeling, modeling and simulation to support translational research, physiologically-based pharmacokinetics (PBPK), model-based meta-analyses of clinical trials, mechanism-based pharmacokinetic-pharmacodynamic modeling, computational pharmacology, bioinformatics, comparative efficacy, effectiveness and cost-effectiveness. Systems pharmacology may involve the application of systems biology approaches to study drug activities, targets and effects. The discipline is often defined with reference to engineering and pharmacological principles as the quantitative analysis of the dynamic interactions between drugs and a biologic system that aims to understand the behavior of the system as a whole. The common focus will be on quantitative methods that improve our understanding of pharmacology and therapeutics in humans.

#### **Abstracting and Indexing**

- · Embase (Elsevier)
- · SCOPUS (Elsevier)
- · MEDLINE/PubMed indexing

#### Society Information

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) was founded in 1900, and consists of over 2,200 professionals whose primary interest is to advance the science and practice of clinical pharmacology and translational medicine for the therapeutic benefit of patients and society. ASCPT is the largest scientific and professional organization serving the disciplines of Clinical Pharmacology and Translational Medicine.

All articles published in this journal are freely available to read, download, and share. Articles are published under the terms of the Creative Commons Attribution Non-Commercial License which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

#### **Disclaimer**

The Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors of the products advertised.

#### Publishe

CPT: Pharmacometrics & Systems Pharmacology is published by Wiley Periodicals, Inc., 101 Station Landing, Suite 300, Medford, MA 02155; Telephone: 781-388-8200; Fax: 781-388-8210.

## CPT: Pharmacometrics & Systems Pharmacology

#### **TUTORIAL**

#### **TUTORIALS**

- 525 NONMEM Tutorial Part I: Description of Commands and Options, With Simple Examples of Population Analysis
  Robert I Bauer
- 538 NONMEM Tutorial Part II: Estimation Methods and Advanced Examples Robert J. Bauer
- **557** ATLAS mPBPK: A MATLAB-Based Tool for Modeling and Simulation of Minimal Physiologically-Based Pharmacokinetic Models

Panteleimon D. Mavroudis, Vivaswath S. Ayyar and William J. Jusko

#### RESEARCH

#### **ARTICLES**

- **567** Physiologically-Based Pharmacokinetic Modeling for the Prediction of CYP2D6-Mediated Gene–Drug–Drug Interactions
  - Flavia Storelli, Jules Desmeules and Youssef Daali
- 577 Optimal Scheduling of Bevacizumab and Pemetrexed/Cisplatin Dosing in Non-Small Cell Lung Cancer Benjamin K. Schneider, Arnaud Boyer, Joseph Ciccolini, Fabrice Barlesi, Kenneth Wang, Sebastien Benzekry and Jonathan P. Mochel
- A Minimal Physiologically-Based Pharmacokinetic Model for Tacrolimus in Living-Donor Liver Transplantation: Perspectives Related to Liver Regeneration and the *cytochrome P450 3A5 (CYP3A5)* Genotype Kotaro Itohara, Ikuko Yano, Tetsunori Tsuzuki, Miwa Uesugi, Shunsaku Nakagawa, Atsushi Yonezawa, Hideaki Okajima, Toshimi Kaido, Shinji Uemoto and Kazuo Matsubara
- 596 Development of a Parsimonious Design for Optimal Classification of Exclusive Breastfeeding Zheng Liu, Aly Diana, Christine Slater, Thomas Preston, Rosalind S. Gibson, Lisa Houghton and Stephen B. Duffull
- 606 Time-to-Event Modeling of Peripheral Neuropathy: Platform Analysis of Eight Valine-Citrulline-Monomethylauristatin E Antibody–Drug Conjugates Matts Kågedal, Divya Samineni, William R. Gillespie, Dan Lu, Bernard M. Fine, Sandhya Girish, Chunze Li and Jin Y. Jin